Journal of the Neurological Sciences xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Influence of timing on electrodiagnosis of Guillain–Barré syndrome in the first six weeks: A retrospective study☆

Yusuf A. Rajabally *, Fu Liong Hiew, John B. Winer

Regional Neuromuscular Clinic, Queen Elizabeth Hospital, University Hospitals of Birmingham, Birmingham, United Kingdom

ARTICLE INFO

Article history:
Received 7 May 2015
Received in revised form 7 July 2015
Accepted 10 July 2015
Available online xxxx

Keywords:
Acute inflammatory demyelinating polyneuropathy
Axonal
Equivocal
Electrophysiology
Guillain–Barré syndrome
Serial

ABSTRACT

The effect of timing is uncertain on the electrophysiology of Guillain–Barré syndrome (GBS). On this may however depend the usefulness of systematic serial studies performed at specific time intervals. We retrospectively analyzed records of 118 consecutive patients with GBS from Birmingham, U.K. (2001–2012), studied between 0–14 days, or, 15–42 days post-onset using new criteria which we recently proposed [4]. Rates of acute inflammatory demyelinating polyneuropathy (AIDP) ($p = 0.45$), axonal GBS ($p = 0.32$) and equivocal forms ($p = 0.46$) were similar for both timings. Similarly, no significant differences between timings were observed using Hadden et al.'s criteria. Proportions were comparable to published serial studies for both timings, for AIDP ($p = 0.25$; $p = 0.10$) and axonal GBS ($p = 0.73$; $p = 0.56$) but were higher than with serial studies for equivocal forms in patients studied on days 0–14 ($p = 0.012$), although not in those studied on days 15–42 ($p = 0.17$). This suggests that over the initial 6 weeks post-onset, timing fails to influence subtype proportions in a large GBS cohort, irrespective of criteria used. Repeat studies appear therefore unlikely to be helpful when systematically performed within this time frame, except in equivocal cases. The benefit of repeat studies remains possible at other times but may need to be individualized, and requires future prospective evaluation.

1. Introduction

The effect of timing on electrophysiology of Guillain–Barré syndrome (GBS) has been the object of several studies in recent years [1,2]. These have consistently demonstrated a change in proportion of GBS subtypes with a described partial shift from acute inflammatory demyelinating polyneuropathy (AIDP) to axonal GBS. The benefit of serial studies has as a result been suggested and considered the gold-standard for diagnosis of GBS subtype. However, serial studies have been performed between 7 and 70 days post-onset rather than at specific time points [1], raising the important issue of most appropriate timing of repeat electrophysiology.

Serial studies were in addition interpreted using criteria for GBS of poor specificity for demyelination and low sensitivity to identify axonal forms [3]. We have since recently proposed new electrophysiological criteria for Guillain–Barré syndrome (GBS) subtypes [4]. These were based on stricter demyelinating cut-offs [5], whose reliability have since been confirmed in multiple populations with chronic inflammatory demyelinating polyneuropathy (CIDP) [6,7]. We in addition utilized new data on axonal GBS subtypes to add parameters in order to increase the detection of this subcategory of patients. With these new proposed criteria [4], proportions of acute inflammatory demyelinating polyneuropathy (AIDP), axonal GBS and equivocal forms were similar to those obtained by other investigators with most informative serial, although non-homogeneously timed studies, using previous criteria [1,2].

The timing of nerve conductions may directly impact on the proportions of subtypes in a GBS cohort, as shown by the previously published serial studies [1,2]. Late electrophysiological results are analyzed as found at a precise moment, irrespective of earlier findings. As a result, global findings at different timings in a large cohort of GBS patients may therefore be helpful in evaluating the potential benefit of serial studies. We here tried to determine the effects of timing on proportions of GBS subtype in different patients having undergone "early" (0–14 days post-disease onset) or "delayed" (15–42 days post-disease onset) studies, in an attempt to ascertain the eventual benefit of serial studies within this time frame.

2. Methods

We retrospectively reviewed our institutional database of patients admitted with a diagnosis of GBS between 2001 and 2012 at the Queen Elizabeth Hospital, Birmingham. The diagnosis was made in each case in accordance with established clinical criteria [8]. Patients included had undergone electrophysiological testing at our center, of at least 3 motor and 2 sensory nerves within 6 weeks of symptom-onset. Electrophysiology was performed according to standard methods by a qualified senior physician trained and experienced in electromyography,

☆ Funding: None.
* Corresponding author at: Regional Neuromuscular Clinic, Queen Elizabeth Hospital, University Hospitals of Birmingham, Birmingham B15 2TH, United Kingdom.
E-mail address: Yusuf.Rajabally@uhb.nhs.uk (Y.A. Rajabally).

http://dx.doi.org/10.1016/j.jns.2015.07.018
0022-510X/

using routine procedures and different neurophysiological equipment over the years of the study. The CMAPs were evoked from the median nerve (stimulating at wrist and elbow, and recording at the *Abductor Pollicis Brevis* muscle), ulnar nerve (stimulating at wrist and below elbow, and recording at the *Abductor Digiti Minimi* muscle), common peroneal nerve (stimulating at ankle and fibular neck and recording at the *Extensor Digitorum Brevis* muscle) and tibial nerve (stimulating at ankle only or ankle and popliteal fossa and recording at the *Abductor Hallucis* muscle). Measured parameters were motor conduction velocity (MCV), distal motor latency (DML), minimum F-wave latency, distal CMAP amplitude and presence of conduction block (CB) as defined within the criteria considered. Results were analyzed with our laboratory's normal values.

Fulfillment of recently described electrodiagnostic criteria was ascertained in each case [4]. We classified patients with AIDP, axonal GBS, or with equivocal electrophysiology and established diagnostic rates. We compared two groups of patients with different timings of electrophysiological studies: "early" (0–14 days post-disease-onset) and "delayed" (15–42 days post-disease-onset). Findings were in addition compared with recent published literature using serial studies [1,2]. We also performed the same process using for diagnostic subtype classification, the electrodiagnostic criteria of Hadden et al. (1998) [3]. Comparison of proportions was performed using Fisher Exact Tests and comparison of means by T-tests. Significance level was set at p values <0.05.

This study, which was part of a larger retrospective analysis of clinical and electrophysiological features of GBS at our institution, was registered and approved by our relevant institutional board (CAD-05169-13, April 2013). Ethics committee approval was not required.

3. Results

We included 118 consecutive patients with a diagnosis of GBS, seen at the Queen Elizabeth Hospital, Birmingham, between 2001 and 2012. Patients were excluded on the basis of incomplete clinical details, delayed electrophysiology performed >42 days after disease onset, insufficiently exhaustive electrophysiology, a diagnosis of Miller Fisher syndrome or a subsequently confirmed diagnosis of acute-onset CIDP. There were 82 males and 36 females. Mean age was 52.1 years (S.D.: 17.8). Mean interval from disease onset to nerve conduction study was 14.4 days (S.D.: 9.3). Seventy-five subjects (54 male, 21 females; mean age 51.2 years [S.D.: 16.6]) were studied between days 1–14 post-disease onset ("early" electrophysiology) and 43 (28 males, 15 females; mean age: 53.7 years [S.D.: 19.6]) were studied between days 15–42 ("delayed" electrophysiology). There were no significant differences in age or gender distribution in between the 2 groups. Mean interval from disease onset to electrophysiological study was 8.8 days (S.D.: 3.5) in the early group and 24.2 days (S.D.: 8.1) for the delayed group. Mean number of motor nerves studied was 4.08 (range: 3–6). Some of the patients in the "delayed" electrophysiology group has been transferred from local district general hospitals to our center for further care and had undergone electrophysiology previously at those other institutions. These initial results were not considered in our analysis. The transferred patients were moved as routinely happens in our region, with occasional delays due to bed availability at our center, resulting in delayed electrophysiology being performed at our unit, as a result. Otherwise, there were also patients who had their first electrophysiological assessment at our institution >14 days post-onset due to delayed primary care referral to the hospital, taking strictly into consideration time of onset which we defined as the start of any motor or sensory symptom. Consequently, there was no overall difference in clinical severity between the early and delayed electrophysiology groups.

Main results and comparative timing data are summarized in Table 1. With newly-proposed criteria [4] and early electrophysiology, 36/75 (48%) had AIDP, 24/75 (32%) had axonal GBS and 15/75 (20%) had an equivocal form. Delayed electrophysiology diagnosed 19/43 (44.2%) of patients with AIDP, 18/43 (41.9%) with axonal GBS and 6/43 (14%) with an equivocal form. Proportions of each subtype were therefore similar for both timing groups (AIDP: $p = 0.71$; axonal GBS: $p = 0.33$; equivocal forms: $p = 0.46$). Comparison with serial studies as reported previously [5,6], showed no difference for either timing group in proportions of AIDP ($p = 0.25$ and $p = 0.18$ respectively) or axonal GBS ($p = 0.25$ and $p = 0.23$ respectively). However proportion of equivocal forms was significantly higher with early electrophysiology than as described with serial studies (15/75 vs. 4/75; $p = 0.012$). This was not the case with delayed electrophysiology (6/43 vs. 4/75; $p = 0.17$).

Hadden et al.'s criteria [3] were met in the early electrophysiology group by 51/75 (68%) for AIDP, 11/75 (14.7%) for axonal GBS and 13/75 (17.4%) for equivocal forms. In the delayed electrophysiology group, these criteria were met by 33/43 (76.7%) for AIDP, 5/43 (11.6%) for axonal GBS and 5/43 (11.6%) for equivocal forms. Proportions of each form were therefore identical for both timing groups (AIDP: $p = 0.40$; axonal GBS: $p = 0.78$; equivocal forms: $p = 0.59$). Also, comparison with the results of the initial electrophysiology as reported in previous studies considered [5,6], showed no difference for either timing group in proportions of AIDP ($p = 0.72$ and $p = 0.67$, respectively), axonal GBS ($p = 0.82$ and $p = 0.78$, respectively), or equivocal forms ($p = 0.65$ and $p = 1$, respectively).

4. Discussion

It appears clear that serial studies may provide important additional information on electrophysiological progression and reveal initially absent abnormalities, or show reversibility of others such as motor or sensory conduction block [1]. However, the main problem that remains is that of their ideal timing. Serial studies as described, have been performed at very variable moments in relation to disease onset. For

Table 1
Comparison of early studies versus delayed studies in 118 consecutive patients with Guillain–Barré syndrome from Birmingham, U.K. (2001–12).

	Early electrophysiology at days 1–14 post-disease-onset [75 patients]	Delayed electrophysiology at days 15–42 post-disease-onset [43 patients]	Comparison of early electrophysiology vs. delayed electrophysiology p values (Fisher Exact Test)
Proportion of AIDP (by Rajabally et al.'s criteria, 2015 [4])	36/75 (48%)	19/43 (44.2%)	0.71
Proportion of axonal GBS (by Rajabally et al.'s criteria, 2015 [4])	24/75 (32%)	18/43 (41.9%)	0.33
Proportion of equivocal cases (by Rajabally et al.'s criteria, 2015 [4])	15/75 (20%)	6/43 (14%)	0.46
Proportion of AIDP (by Hadden et al.'s criteria, 1998 [3])	51/75 (68%)	33/43 (76.7%)	0.40
Proportion of axonal GBS (by Hadden et al.'s criteria, 1998 [3])	11/75 (14.7%)	5/43 (11.6%)	0.78
Proportion of equivocal cases (by Hadden et al.'s criteria, 1998 [3])	13/75 (17.3%)	5/43 (11.6%)	0.59

Please cite this article as: Y.A. Rajabally, et al., Influence of timing on electrodiagnosis of Guillain–Barré syndrome in the first six weeks: A retrospective study, J Neurol Sci (2015), http://dx.doi.org/10.1016/j.jns.2015.07.018

example, they have been done as early as 7 days and as late as 70 days after disease onset [1], with the most informative study used when multiple repeat tests had been done. There is consequently no current scientific rationale regarding the optimal timing of serial studies in GBS.

We have here demonstrated that irrespective of criteria used, proportions of GBS subtypes are not significantly altered in a large cohort, over the initial 6-week post-disease-onset period. This suggests that serial studies, done at specific pre-established time points during this window are unlikely to be helpful in meaningfully altering initial findings, in the overwhelming majority of patients with AIDP and axonal GBS. Interestingly however, and as may be intuitively expected, those with equivocal forms may be usefully re-classified, our results showing significantly higher rates of such cases with early electrophysiology compared to serial studies.

Our analysis has a number of limitations starting with its retrospective design. The long study period, performing of electrophysiolgical studies by a number of different physicians, use of different equipment over the study period, and absence of a formal nerve conduction study protocol, may all have impacted upon the findings. Furthermore, we included in the current study patients who had at least 3 motor nerves studied. This may explain our significantly higher rates of equivocal forms compared to our previous collaborative analysis, where the majority of patients had at least 5 motor nerves tested [4]. This rate is however interestingly perfectly identical to that found by others in applying the newly-proposed criteria, who had, similarly to ourselves in the current analysis, included patients having undergone testing of at least 3 motor nerves (20% vs. 20%; $p = 1$) [9].

Although repeat studies may be helpful in equivocal cases, their timing remains unknown with, given the clinical heterogeneity in GBS, likely considerable and unpredictable inter-individual variability. We believe it is possible that serial electrophysiology may also be helpful in non-equivocal cases in following the progression of individual patients and in studying the pathophysiologic processes involved. However, our current findings raise doubt about repeat studies performed in the 15–42 day timeframe, as is frequently the case in clinical practice. Further large multicentre prospective studies are desirable to determine the place of serial electrophysiology in GBS and may need to focus on later, or different timings in different patient subgroups depending on early findings, immunological results and the clinical progression itself.

References

[1] A. Uncini, C. Manzoli, F. Notturno, M. Capasso, Pitfalls in electrodiagnosis of Guillain–Barré syndrome subtypes, J. Neurol. Neurosurg. Psychiatry 81 (2010) 1157–1163.
[2] N. Shahrizaila, K.J. Goh, S. Abdullah, R. Kuppusamy, N. Yuki, Two sets of nerve conduction studies may suffice in reaching a reliable electrodiagnosis in Guillain–Barré syndrome, Clin. Neurophysiol. 124 (2013) 1456–1459.
[3] R.D.M. Hadden, D.R. Cornblath, R.A.C. Hughes, J. Zilasek, H.P. Hartung, K.V. Toyka, A.V. Swan, the Plasma Exchange/Sandoglobulin Guillain–Barré syndrome Trial Group, Electrophysiological classification of Guillain–Barré syndrome: clinical associations and outcome, Ann. Neurol. 44 (1998) 780–788.
[4] Y.A. Rajabally, M.C. Durand, J. Mitchell, D. Orlikowski, G. Nicolas, Electrophysiological diagnosis of Guillain–Barré syndrome subtype: could a single study suffice? J. Neurol. Neurosurg. Psychiatry 86 (2015) 115–119.
[5] P.Y. Van den Bergh, F. Piéret, Electrodiagnostic criteria for acute and chronic inflammatory demyelinating polyradiculoneuropathy, Muscle Nerve 29 (2004) 565–574.
[6] Y.A. Rajabally, G. Nicolas, F. Piéret, P. Bouche, P.Y. Van den Bergh, Validity of diagnostic criteria for chronic inflammatory demyelinating polyneuropathy: a multicentre European study, J. Neurol. Neurosurg. Psychiatry 80 (2009) 1364–1368.
[7] A. Breiner, T.H. Brannagan III, Comparison of sensitivity and specificity among 15 criteria for chronic inflammatory demyelinating polyneuropathy, Muscle Nerve 50 (2014) 40–46.
[8] B. Wakerley, A. Uncini, Yuki N for the GBS classification group, Nat. Rev. Neurol. 10 (2014) 537–544.
[9] A. Uncini, F. Zappasodi, F. Notturno, Electrodiagnosis of GBS subtypes by a single study: not yet the squaring of the circle, J. Neurol. Neurosurg. Psychiatry 86 (2015) 5–8.

Please cite this article as: Y.A. Rajabally, et al., Influence of timing on electrodiagnosis of Guillain–Barré syndrome in the first six weeks: A retrospective study, J Neurol Sci (2015), http://dx.doi.org/10.1016/j.jns.2015.07.018